

In the ClaimsClaim 1 (Currently amended):

A transgenic mouse whose genome comprises at least one transgene comprising a ~~DNA sequence encoding a normal, mutant, or altered gene~~ nucleic acid sequence encoding a protease inhibitor gene operably linked to a promoter effective for expression of said ~~gene~~ nucleic acid sequence in the brain tissue of said mouse, wherein said transgene is a normal, mutant, or altered gene, and wherein said protease inhibitor interacts with amyloid beta-peptides within the brain tissue of said transgenic mouse.

Claim 2 (Currently amended):

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The transgenic mouse of claim 1, further comprising a second transgene operably linked to a promoter effective for expression of said second transgene, ~~in which~~ wherein said second transgene comprises a ~~DNA sequence encoding a normal, mutant, or altered gene~~ nucleic acid sequence encoding tau-i, apolipoprotein E, APP, presenilin 1, presenilin 2, IL-1 alpha, or IL-1 beta, wherein said second transgene is a normal, mutant, or altered gene, and wherein expression of said nucleic acid sequence encoding said protease inhibitor increases the rate or extent of amyloid formation in the brain tissue of said transgenic mouse.

Claim 3 (Currently amended):

The transgenic mouse of claim 1, wherein the said promoter is a glial fibrillary acidic protein (GFAP) promoter.

Claim 4 (Currently amended):

The transgenic mouse of claim 3, ~~in which~~ wherein said promoter is devoid of ATG start codons.

Claim 5 (Currently amended):

The transgenic mouse of claim 1, wherein ~~the~~ said protease inhibitor is antichymotrypsin (ACT).

Claim 6 (Currently amended):

The progeny of the mouse of claim 1, wherein the genome of said progeny comprises homozygous or heterozygous alleles of human antichymotrypsin (ACT) gene.

Claim 7 (Currently amended):

A primary cell culture or cell line ~~derived~~ established from the mouse of claim 1.

Claim 8 (Currently amended):

The transgenic mouse of ~~claim 1, in which the~~ claim 2, wherein expression of said ~~ACT gene~~ nucleic acid sequence encoding said protease inhibitor produces symptoms of a disease that is essentially similar to a human Alzheimer's disease or amyloidogenic disease.

Claim 9 (Currently amended):

The transgenic mouse of claim 8, wherein said amyloidogenic disease is selected from the group consisting of scrapie, transmissible spongiform encephalopathies (TSE's), hereditary cerebral hemorrhage with amyloidosis Icelandic-type (HCHWA-I), hereditary cerebral hemorrhage with amyloidosis Dutch-type (HCHWA-D), Familial Mediterranean Fever, Familial amyloid nephropathy with urticaria and deafness (Muckle-Wells syndrome), myeloma or macroglobulinemia-associated neuropathy associated with amyloid, Familial amyloid polyneuropathy (Portuguese), Familial amyloid cardiomyopathy (Danish), Systemic senile amyloidosis, Familial amyloid polyneuropathy (Iowa), Familial amyloidosis (Finnish), Gerstmann-Sträussler-Scheinker syndrome, Medullary carcinoma of thyroid, Isolated atrial amyloid, Islets of Langerhans, Diabetes type II, and Insulinoma.

Claim 10 (Original):

A method of screening a compound suspected of having utility for treating Alzheimer's disease or amyloidogenic disease, said method comprising: providing the transgenic mouse of claim 1; administering said compound to said mouse; and monitoring a pathological or cognitive marker of said disease.

Claim 11 (Cancelled)Claim 12 (Original):

A method of screening a compound suspected of inhibiting or promoting phosphorylation of one or more proteins associated with Alzheimer's disease, said method comprising: providing the transgenic mouse of claim 1; administering said compound to said mouse; and monitoring the phosphorylation state of said one or more proteins.

Claim 13 (Currently amended):

The method of claim 12, ~~in which~~ wherein said protein is selected from the group consisting of an endogenous mouse tau protein, a product of a human tau transgene, ~~or~~ and a mitosis specific protein.

Claim 14 (Currently amended):

The method of claim 12, ~~in which~~ wherein said protein is ~~an~~ selected from the group consisting of APP, cdc-2/cyclin B, cdk5, p53, cdc47, MAD, cyclin D, or and cyclin E.

Claim 15 (Original):

A method of screening a compound suspected of inhibiting or promoting formation or aggregation of abnormal protein filaments within a neuron or neuronal process, said method comprising: providing the transgenic mouse of claim 1; administering said compound to said mouse; and monitoring the formation or aggregation of said filament.

Claim 16 (Original):

A method of screening a compound suspected of inhibiting or promoting the development of neuronal cell death or synapse loss, said method comprising: providing the transgenic mouse of claim 1; administering said compound to said mouse; and monitoring said neuronal cell death or synapse loss.

Claim 17 (Currently amended):

01 The method of claim 16, ~~in which~~ wherein said neuronal cell death or synapse loss is monitored by TUNEL staining, neurofilament antibody staining, or synaptophysin antibody staining.

Claim 18 (Original):

A method for testing a compound suspected of promoting or inhibiting phosphorylation of one or more proteins related to Alzheimer's disease, said method comprising: providing a mammalian cell; administering to said cell antichymotrypsin and said compound; and monitoring the phosphorylation state of said one or more proteins.

Claim 19 (Currently amended):

The method of claim 18, ~~in which~~ wherein said protein is tau, APP, cdc-2/cyclin B, cdk5, p53, cdc47, MAD, cyclin D, or cyclin E.

Claim 20 (Currently amended):

A method for testing a compound suspected of promoting or inhibiting the activity of a protease inhibitor to promote or inhibit cell death or cell division, said method comprising: providing a mammalian cell; administering to said cell antichymotrypsin and said compound; ~~and~~ monitoring cell death or cell division; and determining whether the compound promotes or inhibits the activity of the protease inhibitor to promote or inhibit cell death or cell division.

Claim 21 (Currently amended):

A method for testing a compound suspected of promoting or inhibiting the activity of a protease inhibitor to promote or inhibit neurite outgrowth, said method comprising: providing a mammalian neuronal cell; administering to said cell antichymotrypsin and said compound; and monitoring said neurite outgrowth; and determining whether the compound promotes or inhibits the activity of the protease inhibitor to promote or inhibit neurite outgrowth.

Claim 22 (Currently amended):

Ca The method of claim 18, ~~in which~~ wherein said cell is neuronal.

Claim 23 (Cancelled)Claim 24 (Currently amended):

A method for measuring the effect on cognitive function in a ~~transgenic animal~~ transgenic mouse of a compound suspected of having utility in the treatment or prevention of Alzheimer's disease, said method comprising: providing a first group and a second group of transgenic mice that are an animal model of Alzheimer's disease; administering said compound to each mouse in said first group; and measuring the cognitive function of each said mouse in said first and second group in a radial arm water maze having an escape platform capable of relocation among the radial arms of said maze.

Claim 25 (Currently amended):

The method of claim 24, ~~in which each said transgenic mouse~~ wherein each of said transgenic mice further comprises a normal, mutant, or homologous transgene comprising a nucleic acid sequence encoding a protease inhibitor, and wherein said protease inhibitor interacts with amyloid beta-peptides within the brain tissue of each of said transgenic mice.

Claim 26 (Currently amended):

The method of claim 25, ~~in which~~ wherein said protease inhibitor is antichymotrypsin.

Claim 27 (Currently amended):

The method of claim 25, ~~in which~~ wherein said protease inhibitor is anti-trypsin, alpha-2-macroglobulin, BACE, or a Kunitz inhibitor-containing protein.

Claim 28 (Currently amended):

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The method of claim 24, ~~in which~~ wherein said compound suspected of having utility in the treatment of Alzheimer's disease is selected from the group consisting of an anti-inflammatory agent, an inhibitor of an interaction between A-beta peptide and antichymotrypsin, an inhibitor of an interaction between A-beta peptide and apolipoprotein E, an inhibitor of antichymotrypsin expression, an inhibitor of apolipoprotein E expression, an inhibitor of APP expression, ~~or~~ and an inhibitor of expression of an A-beta peptide.

Claim 29 (New)

A transgenic mouse whose genome comprises at least one transgene comprising a nucleic acid sequence encoding antichymotrypsin (ACT) operably linked to a promoter effective for expression of said nucleic acid sequence in the brain tissue of said transgenic mouse, wherein said transgene is a normal, mutant, or altered gene.

Claim 30 (New):

The transgenic mouse of claim 29, further comprising a second transgene operably linked to a promoter effective for expression of said second transgene, in which said second transgene comprises a DNA sequence encoding a normal, mutant, or altered gene encoding tau-i, apolipoprotein E, APP, presenilin 1, presenilin 2, IL-1 alpha, or IL-1 beta, and wherein expression of said nucleic acid sequence encoding said ACT increases the rate or extent of amyloid formation in the brain tissue of said transgenic mouse.

Claim 31 (New):

The transgenic mouse of claim 29, wherein said promoter is effective for expression of said nucleic acid sequence in astrocytes within the brain tissue of said transgenic mouse.

Claim 32 (New):

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The transgenic mouse of claim 30, wherein said promoter is effective for expression of said nucleic acid sequence encoding said antichymotrypsin (ACT) in astrocytes within the brain tissue of said transgenic mouse

Claim 33 (New):

The transgenic mouse of claim 29, wherein said promoter is a glial fibrillary acidic protein (GFAP) promoter.

Claim 34 (New):

The transgenic mouse of claim 33, wherein said GFAP promoter is devoid of ATG start codons.

Claim 35 (New):

The transgenic mouse of claim 29, wherein said nucleic acid sequence encodes a normal gene encoding antichymotrypsin.

Claim 36 (New):

The transgenic mouse of claim 30, wherein expression of said nucleic acid sequence encoding said antichymotrypsin (ACT) produces symptoms of a disease that is essentially similar to a human Alzheimer's disease or amyloidogenic disease.

Claim 37 (New):

The progeny of the mouse of claim 2, wherein the genome of said progeny comprises homozygous or heterozygous alleles of human antichymotrypsin (ACT) gene.

Claim 38 (New):

The progeny of the mouse of claim 29, wherein the genome of said progeny comprises homozygous or heterozygous alleles of human antichymotrypsin (ACT) gene.

Claim 39 (New):

The progeny of the mouse of claim 30, wherein the genome of said progeny comprises homozygous or heterozygous alleles of human antichymotrypsin (ACT) gene.

Claim 40 (New):

A primary cell culture or cell line established from the mouse of claim 2.

Claim 41 (New):

A primary cell culture or cell line established from the mouse of claim 29.

Claim 42 (New):

A primary cell culture or cell line established from the mouse of claim 30.

Claim 43 (New):

A transgenic mouse whose genome comprises at least one transgene comprising a nucleic acid sequence encoding a protease inhibitor operably linked to a glial fibrillary acidic protein (GFAP) promoter effective for expression of said nucleic acid sequence in the brain tissue of said transgenic mouse, wherein said protease inhibitor interacts with amyloid beta-peptides within the brain tissue of said transgenic mouse, and wherein said protease inhibitor is selected from the group consisting of antichymotrypsin (ACT), antitrypsin, and alpha-2 macroglobulin.

Claim 44 (New):

The transgenic mouse of claim 43, wherein said protease inhibitor is antichymotrypsin (ACT).

Claim 45 (New):

A transgenic mouse whose genome comprises at least one transgene comprising a nucleic acid sequence encoding antichymotrypsin (ACT) operably linked to a glial fibrillary acidic protein (GFAP) promoter effective for expression of said nucleic acid sequence in astrocytes within the brain tissue of said mouse, wherein said GFAP promoter is devoid of ATG start codons.

Claim 46 (New):

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A transgenic mouse whose genome comprises at least one transgene comprising a nucleic acid sequence encoding antichymotrypsin (ACT) operably linked to a glial fibrillary acidic protein (GFAP) promoter effective for expression of said nucleic acid sequence in the brain tissue of said transgenic mouse, and wherein said genome comprises a second transgene operably linked to a promoter effective for expression of said second transgene, in which said second transgene comprises a nucleic acid sequence encoding a normal, mutant, or altered gene encoding tau-i, apolipoprotein E, APP, presenilin 1, presenilin 2, IL-1 alpha, or IL-1 beta, and wherein expression of said nucleic acid sequence encoding said ACT increases the rate or extent of amyloid formation in the brain tissue of said transgenic mouse.
